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NOVEL SULFENAMIDES

Technical Field

The present invention relates to novel sulfenamides that have an antimicrobial action, methods for their synthesis, pharmaceutical compositions containing them and method of treatment of patients suffering microbial infection.

Background Art

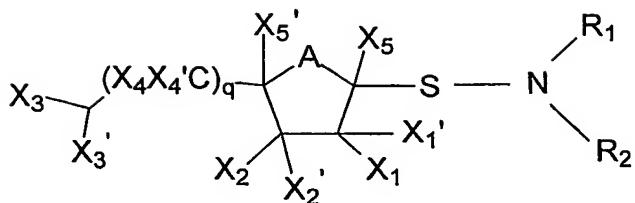
Many bacterial diseases once thought to be on the decline are beginning to re-emerge and annually devastate populations in many countries. This problem is amplified by the emergence of many new drug resistant strains of the microorganisms that cause these diseases. Our interest in glycofuranose chemistry (Owen & von Itzstein, 2000) has led to the discovery of a new class of antimicrobial agents described below. Although significant chemistry and biology has been published (see, for example, Marino, Marino, Milette, Alves, Colli, & de Lederkremer, 1998; Milette, Marino, Marino, de Lederkremer, Colli & Alves, 1999; Zhang & Liu, 2001; Brimacombe, Gent & Stacey, 1968; Brimacombe, Da'aboul & Tucker, 1971; Lemieux & Stick, 1975; de Lederkremer, Cirelli & Sznaidman, 1986; Shin & Perlin, 1979; de Lederkremer, Cicero & Varela, 1990; de Lederkremer, Marino & Marino, 2002; Pathak, Pathak, Suling, Gurcha, Morehouse, Besra, Maddry & Reynolds, 2002; Ernst, Hart & Sinay, 2000) in the area of glycofuranose chemistry and biology none to date have provided compounds that are clinically useful antimicrobial medicines.

Disclosure of the Invention

The present invention is concerned generally with novel sulfenamides.

In a first aspect of the present invention there is provided a compound of general formula (I):

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wherein A is selected from the group consisting of O, S, SO, Se, Te, NR₈, CR₉R'₉, N → O and C(O);

5 and, when A is O and q is 1, one of R₁ and R₂ is selected from the group consisting of hydrogen, optionally substituted C₁₋₃ or >C₃₀ alkyl, alkyl when interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted C₂₋₃ or >C₃₀ alkenyl, alkenyl when interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more 10 heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclic and a carbohydrate moiety, while the other of R₁ and R₂ is selected from the 15 group consisting of hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted alkenyl which may be interrupted by one or more 20 heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O, 25 S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted aralkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted 30 aryl, optionally substituted heterocyclic, optionally substituted acyl and a carbohydrate moiety;

but, when A is S, SO, SO₂, Se, Te, NR₈, CR₉R'₉, N

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→ O or C(O) and q is 1 or A is O, S, SO, Se, Te, NR₈, CR₉R₉', N → O or C(O) and q is 0, then R₁ and R₂ are independently selected from the group consisting of hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted alkenyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted aryl, optionally substituted acyl and a carbohydrate moiety, or R₁ and R₂ together with the nitrogen atom from which they depend form a saturated or unsaturated, optionally substituted heterocyclic group which may include additional heteroatoms selected from the group consisting of O, N and S;

X₁ is selected from the group consisting of OR₃, SR₃, NR₃R'₃, hydrogen, halogen, -(Y)_mC=(Z)(T)_nR₃, -N(C=(Z)(T)_nR₃)₂, N₃, CN, OCN, SCN, OSO₃R₃, OSO₂R₃, OPO₃R₃R'₃, OPO₂R₃R'₃, S(O)R₃, S(O)₂R₃, S(O)₂OR₃, PO₃R₃R'₃, NR₃NR'₃R''₃, SNR₃R'₃, NR₃SR'₃, SSR₃ and R₃, or is an oxo group, =S, =NOR₃ or =CR₃R'₃ and X₁' is absent;

X₂ is selected from the group consisting of OR₄, SR₄, NR₄R'₄, hydrogen, halogen, -(Y)_mC=(Z)(T)_nR₄, -N(C=(Z)(T)_nR₄)₂, N₃, CN, OCN, SCN, OSO₃R₄, OSO₂R₄, OPO₃R₄R'₄, OPO₂R₄R'₄, S(O)R₄, S(O)₂R₄, S(O)₂OR₄, PO₃R₄R'₄, NR₄NR'₄R''₄, SNR₄R'₄, NR₄SR'₄, SSR₄ and R₄, or is an oxo group, =S, =NOR₄ or =CR₄R'₄ and X₂' is absent;

X₃ and X₃' are independently selected from the group consisting of OR₅, SR₅, NR₅R'₅, hydrogen, halogen, -(Y)_mC=(Z)(T)_nR₅, -N(C=(Z)(T)_nR₅)₂, N₃, CN, OCN, SCN, OSO₃R₅, OSO₂R₅, OPO₃R₅R'₅, OPO₂R₅R'₅, S(O)R₅, S(O)₂R₅, S(O)₂OR₅, PO₃R₅R'₅, NR₅NR'₅R''₅, SNR₅R'₅, NR₅SR'₅, SSR₅ and R₅, or X₃ is

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=O, =S, =NOR₅ or =CR₅R'₅ and X₃' is absent;

X₄ is selected from the group consisting of OR₆, SR₆, NR₆R'₆, hydrogen, halogen, -(Y)_mC=(Z)(T)_nR₆, -N(C=(Z)(T)_nR₆)₂, N₃, CN, OCN, SCN, OSO₃R₆, OSO₂R₆, OPO₃R₆R'₆, 5 OPO₂R₆R'₆, S(O)R₆, S(O)₂R₆, S(O)₂OR₆, PO₃R₆R'₆, NR₆NR'₆R''₆, SNR₆R'₆, NR₆SR'₆, SSR₆ and R₆, or is an oxo group, =S, =NOR₆ or =CR₆R'₆ and X₄' is absent;

X₅ is selected from the group consisting of hydrogen, CN, -C=(Z)(T)_nR₁₁, S(O)R₁₁, S(O)₂R₁₁, S(O)₂OR₁₁, 10 PO₃R₁₁R'₁₁, optionally substituted alkyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl;

X₁', X₂', X₄' and X₅' are the same or different 15 and are selected from the group consisting of hydrogen, CN, optionally substituted alkyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl;

or one of X₁ and X₂, X₂ and X₅', X₅' and A when A 20 contains a carbon or nitrogen atom, X₅ and A when A contains a carbon or nitrogen atom, and X₅ and X₁ together constitute a double bond, or X₅' and X₄ or X₃ and X₄ together constitute a double bond, or R₁ and X₁, R₂ and X₁, R₁ and X₂, R₂ and X₂, R₁ and X₅, R₂ and X₅, R₁ and X₅', R₂ and 25 X₅', X₁ and X₂, X₂ and X₃, X₂ and X₄, X₃ and X₄, X₁ and X₁', X₂ and X₂', X₃ and X₃' or X₄ and X₄' together form part of a ring structure which optionally includes at least one heteroatom selected from O, S and N and is optionally substituted;

30 m, n and q are independently 0 or 1 and Y, Z and T are independently selected from the group consisting of O, S, and NR₁₀;

R₃, R'₃, R''₃, R₄, R'₄, R''₄, R₅, R'₅, R''₅, R₆, R'₆, R''₆, R₇, R₈, R₉, R'₉, R₁₀, R₁₁ and R'₁₁ are the same or 35 different and are selected from the group consisting of hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional

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groups selected from the group consisting of O, S, -N=, NR,
and -(Y)_nC=(Z)(T)_n-, optionally substituted alkenyl which
may be interrupted by one or more heteroatoms or
functional groups selected from the group consisting of O,
5 S, -N=, NR, and -(Y)_nC=(Z)(T)_n-, optionally substituted
aryl, optionally substituted aralkyl which may be
interrupted within the alkyl moiety by one or more
heteroatoms or functional groups selected from the group
consisting of O, S, -N=, NR, and -(Y)_nC=(Z)(T)_n-,
10 optionally substituted acyl and a carbohydrate moiety;
with the proviso that at least two of X₁, X₂, X₃
and X₄ are other than hydrogen or a group linked to the
ring through a carbon-carbon bond and the further proviso
that the compound of general formula (I) is not 1-(9H-
15 purinyl)-S-(3-deoxy-pentafuranosyl)sulfenamide
5-formamido-2',3',5'-tri-O-formyl-1-(β-D-
ribofuranosylthio)imidazole-4-carboxamide,
N-phenyl-S-(2,3:5,6-di-O-isopropylidene-β-D-
mannofuranosyl)sulfenamide or
20 N,N-diethyl-S-(2,3,5,6-tetra-O-benzoyl-β-D-
galactofuranosyl)sulfenamide;

or a pharmaceutically acceptable salt thereof.

It will be appreciated that the manner of
representing substituents in the foregoing general formula
25 does imply any particular stereochemistry or orientation
for the substituents.

The term "alkyl" used either alone or in a
compound word such as "optionally substituted alkyl" or
"optionally substituted cycloalkyl" denotes straight
30 chain, branched or mono- or poly- cyclic alkyl. Examples
of straight chain and branched C alkyl include methyl.
ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl,
tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl,
1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl,
35 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-
dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-
dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-

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trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl,
2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-
dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl,
1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-
5 trimethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-
methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-2- or 3-
propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-
methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-,
3- or 4-propylheptyl, undecyl 1-, 2-, 3-, 4-, 5-, 6-, 7-,
10 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-
ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-
butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-,
6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-
15 , 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propynonyl,
1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like.
Examples of cycloalkyl include cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl,
cyclononyl and cyclodecyl and the like.

The term "alkenyl" used either alone or in
20 compound words such as "alkenyloxy" denotes groups formed
from straight chain, branched or cyclic alkenes including
ethylenically mono-, di- or poly-unsaturated alkyl or
cycloalkyl groups as defined above. Examples of C₄-30
alkenyl include butenyl, iso-butenyl, 3-methyl-2-butenyl,
25 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-
hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl,
1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl,
1-decenyl, 3-decenyl, 1,3-butadienyl, 1-4,pentadienyl,
1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-
30 cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-
cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-
cyclooctatetraenyl.

The term "acyl" used either alone or in compound
words such as "optionally substituted acyl" or "optionally
35 substituted acyloxy" denotes an aliphatic acyl group or an
acyl group containing an aromatic ring, which is referred
to as aromatic acyl, or a heterocyclic ring, which is

referred to as heterocyclic acyl, preferably C₁₋₃₀ acyl. Examples of acyl include straight chain or branched alkanoyl such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, 5 hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; cycloalkylcarbonyl such as cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, 10 naphthylpropanoyl and naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacrylyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); heterocycliccarbonyl, 15 heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl; and heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, 20 heterocyclicpentenoyl and heterocyclichexenoyl.

The term "aryl" used either alone or in compound words such as "optionally substituted aryl", "optionally substituted aryloxy" or "optionally substituted heteroaryl" denotes single, polynuclear, conjugated and 30 fused residues of aromatic hydrocarbons ("carbocyclic aryl" or "carboaryl") or aromatic heterocyclic (heteroaryl") ring systems. Examples of carbocyclic aryl include phenyl, biphenyl, terphenyl, quaterphenyl, phenoxyphenyl, naphtyl, tetrahydronaphthyl, anthracenyl, 35 dihydroanthracenyl, benzantracenyl, dibenzanthracenyl, phenanthrenyl, fluorenlyl, pyrenyl, indenyl, azulenyl, chrysensyl, Examples of heteroaryl include pyridyl, 4-

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phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrryl,
pyrrolyl, furanyl, imadazolyl, pyrrolydanyl, pyridinyl,
piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl,
thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl,
5 benzofuranyl, benzothienyl, purinyl, quinazolinyl,
phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and
the like. Preferably, a carbocyclic aromatic ring system
contains 6-10 carbon atoms and an aromatic heterocyclic
ring system contains 1 to 4 heteratoms independently
10 selected from N, O and S and up to 9 carbon atoms in the
ring.

The term "heterocyclyl" or equivalent terms such
as "heterocyclic" used either alone or in compound words
such as "optionally substituted saturated or unsaturated
15 heterocyclyl" denotes monocyclic or polycyclic
heterocyclyl groups containing at least one heteroatom
atom selected from nitrogen, sulphur and oxygen. Suitable
heterocyclyl groups include N-containing heterocyclic
groups, such as, unsaturated 3 to 6 membered
20 heteromonocyclic groups containing 1 to 4 nitrogen atoms,
for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl,
pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or
tetrazolyl;

saturated 3 to 6-membered heteromonocyclic groups
25 containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl,
imidazolidinyl, piperidino or piperazinyl;

unsaturated condensed heterocyclic groups
containing 1 to 5 nitrogen atoms, such as indolyl,
isoindolyl, indolizinyl, benzimidazolyl, quinolyl,
30 isoquinolyl, indazolyl, benzotriazolyl or
tetrazolopyridazinyl;

unsaturated 3 to 6-membered heteromonocyclic
group containing an oxygen atom, such as, oxiranyl,
pyranyl or furyl;

35 unsaturated 3 to 6-membered heteromonocyclic
group containing 1 to 2 sulfur atoms, such as, thienyl;
unsaturated 3 to 6-membered heteromonocyclic

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group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms,
5 such as, morpholinyl;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;

unsaturated 3 to 6-membered heteromonocyclic
10 group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl or thiadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl; and

15 unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

The term "carbohydrate" denotes a carbohydrate residue or a functionalised or deoxygenated carbohydrate residue, and includes monosaccharides and oligosaccharides. A carbohydrate residue is an acyclic polyhydroxy-aldehyde or ketone, or one of their cyclic tautomers, and includes a compound resulting from reduction of the aldehyde or keto group such as alditols. Oxygen atoms may be replaced by hydrogen or bonds to a halogen, nitrogen, sulfur or carbon atoms, or carbon-oxygen bonds such as in ethers or esters may be introduced. Examples of carbohydrates include but are not limited to D-galactofuranose, N-acetyl-D-galactofuranose, D-glucofuranose, N-acetyl-D-glucofuranose, D-galactopyranose N-acetyl-D-galactopyranose, D-glucopyranose and N-acetyl-D-glucopyranose and their equivalents where oxygen atoms have been replaced in selected positions with hydrogen or bonds to halogen, nitrogen, sulfur or carbon, as well as oligosaccharides containing these moieties.

In this specification "optionally substituted" means that a group may or may not be further substituted

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with one or more functional groups such as alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloarylloxy; nitro,
5 nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, benzylamino, dibenzylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, diacylamino, acyloxy,
10 alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy, heterocyclamino, halo(heterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, alkylthio, benzylthio, acylthio, phosphorus-containing groups and the like, and including groups such
15 as =O, =S, =N-, where appropriate, particularly as substituents in ring structures such as lactones, lactams and cyclic imides, provided that none of the substituents outlined above interferes with the formation of the subject compound.

20 Any of the moieties whose length is defined in terms of the number of carbon atoms present may possess any number of carbon atoms within the specified range. Nevertheless, within this range certain species will be preferred due to factors such as availability and cost of
25 precursors and ease of synthesis, as well as efficacy.

In an embodiment A is O and q is 1 and one of R₁ and R₂ is selected from the group consisting of hydrogen, optionally substituted C₁₋₃ or >C₃₀ alkyl, alkyl when interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted C₂₋₃ or >C₃₀ alkenyl, alkenyl when interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, 30 optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O,
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S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclic and a carbohydrate moiety, while the other of R₁ and R₂ is selected from the group consisting of

5 hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted alkenyl which may be interrupted by one or more heteroatoms or

10 functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -

15 (Y)_mC=(Z)(T)_n-, optionally substituted aryl, optionally substituted heterocyclic, optionally substituted acyl and a carbohydrate moiety.

In an alternative embodiment A is S, SO, SO₂, Se, Te, NR₈, CR₉R_{9'}, N → O or C(O) and q is 1 or A is O, S, SO, SO₂, Se, Te, NR₈, CR₉R_{9'}, N → O or C(O) and q is 0, and R₁ and R₂ are independently selected from the group consisting of hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted alkenyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -(Y)_mC=(Z)(T)_n-, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR₇ and -

25 (Y)_mC=(Z)(T)_n-, optionally substituted aryl, optionally substituted acyl and a carbohydrate moiety, or R₁ and R₂ together with the nitrogen atom from which they depend form a saturated or unsaturated, optionally substituted heterocyclic group which may include additional

30 heteroatoms selected from the group consisting of O, N and

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S.

In an embodiment when R₁ and R₂ are independently C₄₋₃₀ alkyl, and may be C₆₋₁₂ alkyl and/or C₈₋₁₀ alkyl. If one or both R₁ and R₂ is alkenyl it may be C₄₋₃₀ alkenyl, in a further embodiment C₆₋₁₂ alkenyl and, in a further embodiment still, C₈₋₁₀ alkenyl. In the case of one or both R₁ and R₂ being or including alkyl or alkenyl interrupted by one or more of heteroatoms or functional groups, the heteroatom is typically oxygen, and R₁ and/or R₂ may have the formula CH₃(CH₂)_xO(CH₂)_yO(CH₂)_z. Equally, if one of R₃, R'₃, R''₃, R₄, R'₄, R''₄, R₅, R'₅, R''₅, R₆, R'₆, R''₆, R₇, R₈, R₉, R'₉, R₁₀, R₁₁ and R'₁₁ is alkyl, alkenyl or alkyl or alkenyl interrupted by one or more of heteroatoms or functional groups the preferred forms are as set out for R₁ and R₂.

In an embodiment the amine portion of the sulfenamide is tethered to the carbohydrate moiety through an additional linkage, for example, if the amine per se were toxic in order to ensure it is not released by *in vivo* cleavage of the sulfenamide linkage. While the amine moiety may be tethered by linkage to any position in the carbohydrate moiety, linkage to the C₂ position through either R₁ or R₂ forming a ring together with X₁ is preferred. By way of example only, the linkage may take the form of an optionally substituted alkyl chain being linked to end of a functional group located in position 2 of the carbohydrate ring and linked to a functional group located within R₁ or R₂.

In an embodiment X₁ is OR₃. Advantageously R₃ is hydrogen or optionally substituted acyl.

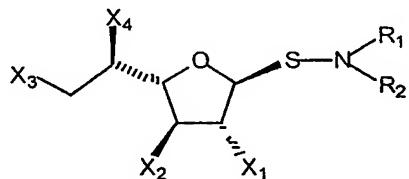
In an embodiment X₂ is OR₄. Advantageously, R₄ is hydrogen or optionally substituted acyl.

In an embodiment X₃ is OR₅. Advantageously, R₅ is hydrogen or optionally substituted acyl.

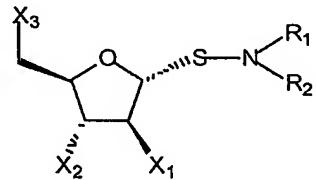
In an embodiment X₄, when present, is OR₆. Advantageously, R₆ is hydrogen or optionally substituted acyl.

In an embodiment any one of the substituents R₃, R₄, R₅ and R₆ is optionally substituted acyl, in particular, optionally substituted acyl where the substituent on the acyl group effects the lipophilicity or water solubility 5 of the compound. By way of example, preferred compounds include amino acid esters where the amino acid side chain is selected to provide a predetermined lipophilicity for the compound. The amino acid side chains envisaged include all of the natural occurring amino acid side 10 chains as well as common synthetic amino acids. Alternatively, the compounds maybe succinyl esters terminating in amides that improve water solubility.

In an embodiment the compounds of the invention are galactofuranosyl compounds, and therefore have the 15 configuration illustrated in general formula (Ia) :



In a further embodiment the compounds of the 20 invention are arabinofuranosyl derivatives having the general formula (Ib) :



Advantageously the sulfenamide of general formula 25 (I) is selected from the group consisting of N-benzyl-S-(2,3,5,6-tetra-O-benzoyl-β-D-galactofuranosyl)-sulfenamide, N,N-dibenzyl-S-(2,3,5,6-tetra-O-acetyl-β-D-galactofuranosyl)sulfenamide, N,N-dicyclohexyl-S-(2,3,5,6-tetra-O-acetyl-β-D-galactofuranosyl)sulfenamide, 30 N,N-di(2-methoxyethoxyethyl)-S-(2,3,5,6-tetra-O-acetyl-β-D-

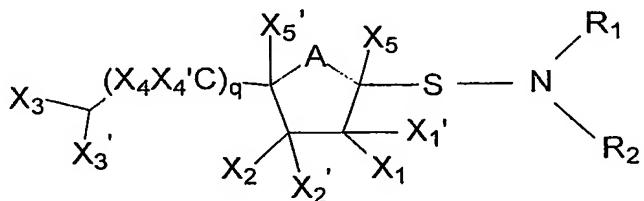
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galactofuranosyl) sulfenamide, 1-(2,2,6,6-tetramethyl-piperidinyl)-S-(2,3,5,6-tetra-O-acetyl- β -D-galactofuranosyl) sulfenamide, N,N-dioctyl-S-(2,3-di-O-acetyl-5-O-[tert-butyldiphenylsilyl]- α -D-arabinofuranosyl) sulfenamide, N,N-dibenzyl-S-(β -D-galactofuranosyl) sulfenamide, and N,N-di(2-methoxyethoxyethyl)-S-(β -D-galactofuranosyl) sulfenamide.

In a particularly preferred embodiment of the invention the compound of general formula (I) is N,N-dibenzyl-S-(β -D-galactofuranosyl) sulfenamide or N,N-di(2-methoxyethoxyethyl)-S-(β -D-galactofuranosyl) sulfenamide.

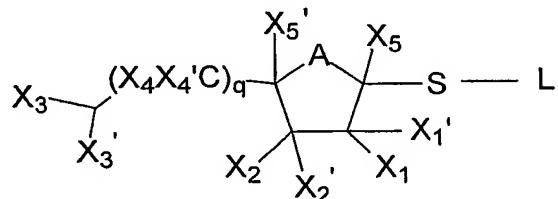
According to a second aspect of the present invention there is provided a method of preparation of a compound of general formula (I) :

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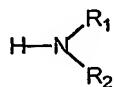
comprising reacting a compound of general formula (II) :

20



wherein L is a leaving group, preferably acetyl and X₁, X_{1'}, X₂, X_{2'}, X₃, X_{3'}, X₄, X_{4'}, X₅ and X_{5'}, are as defined above;

25 with a compound of general formula (III) :



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wherein R₁ and R₂ are as defined above;
in the presence of a bis-activated alkyl halide.
Typically the bis-activated alkyl halide is
diethyl bromomalonate, trimethyl bromophosphonoacetate or
5 N-bromosuccinimide. In general terms the reaction is
performed in the presence of an excess of the secondary
amine of general formula (III) in an inert solvent such as
DMF or THF, in an alcoholic solvent such as methanol or
ethanol, or in mixtures of such solvents, at a temperature
10 from 20°C to 60°C, preferably 25°C to 40°C, under an
atmosphere of nitrogen or argon. The reaction mixture may
be left to stir typically for 2 to 160 hours, preferably
greater than 12 hours, prior to isolation and
purification, or deprotection. In an embodiment, R₂, R'₂,
15 R''₂, R₃, R'₃, R''₃, R₄, R'₄, R''₄, R₅, R'₅, R''₅, R₆, R'₆ and
R''₆ may be a protecting group and the process then further
comprises removing the protecting groups. Suitable
protecting groups are well known to the person skilled in
the art and in this case the acetyl or benzoyl groups are
20 preferred. Acetyl and benzoyl protecting groups are
typically removed through hydrolysis with sodium methoxide
in methanol. The compounds of the present invention may
also be synthesised through the condensation of sulphenyl
halides with a secondary amine of general formula (III),
25 the reaction of the relevant thiols and amines in the
presence of oxidising reagents, or via the reaction of the
relevant disulfides or thiosulfonates and amines in the
presence of silver or mercuric salts, such as are
disclosed in Craine & Raban, 1989; Koval', 1996; Illyés,
30 2004; the contents of which are incorporated herein by
reference. An extensive array of methodologies has been
developed to manipulate each position of the furanose
template as disclosed, for example, in Marino, Marino,
Miletti, Alves, Colli, & de Lederkremer, 1998; Miletti,
35 Marino, Marino, de Lederkremer, Colli & Alves, 1999; Zhang
& Liu, 2001; Brimacombe, Gent & Stacey, 1968; Brimacombe,
Da'aboul & Tucker, 1971; Lemieux & Stick, 1975; de

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Lederkremer, Cirelli & Sznajdman, 1986; Shin & Perlin, 1979; de Lederkremer, Cicero & Varela, 1990; de Lederkremer, Marino & Marino, 2002; Pathak, Pathak, Suling, Gurcha, Morehouse, Besra, Maddry & Reynolds, 2002; 5 Ernst, Hart & Sinay, 2000; the contents of which are incorporated herein by reference.

According to a third aspect of the present invention there is provided a method for the treatment of a patient with a microbial infection, comprising 10 administering to said patient a therapeutically effective amount of a compound of general formula (I).

According to a fourth aspect of the present invention there is provided the use of a compound of 15 general formula (I) in the manufacture of a medicament for use in the treatment of a microbial infection.

As used herein, the term "therapeutically effective amount" means an amount of a compound of the present invention effective to yield a desired therapeutic response, for example to prevent or treat a disease which 20 by administration of a pharmaceutically-active agent.

The specific "therapeutically effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition and clinical history of the subject, the type of animal being 25 treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compound or its derivatives.

As used herein, a "pharmaceutical carrier" is a 30 pharmaceutically acceptable solvent, suspending agent, excipient or vehicle for delivering the compound of general formula (I) to the subject. The carrier may be liquid or solid, and is selected with the planned manner of administration in mind.

35 The compound of general formula (I) may be administered orally, topically, or parenterally in dosage unit formulations containing conventional non-toxic

pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrathecal, intracranial, injection or infusion techniques.

5 The invention also provides suitable topical, oral, aerosol, and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compounds of the invention may be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use may contain one or more agents selected from the group of sweetening agents, flavouring agents, colouring agents and preserving agents in order to produce 10 pharmaceutically elegant and palatable preparations. The tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.

15

These excipients may be, for example, inert 20 diluents, such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as corn starch or alginic acid; binding agents, such as starch, gelatin or acacia; or lubricating agents, such as magnesium stearate, stearic acid or talc. The tablets may be uncoated, or may be 25 coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. 30 Coating may also be performed using techniques described in the U. S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

The compound of general formula (I) of the 35 invention can be administered, for *in vivo* application, parenterally by injection or by gradual perfusion over time independently or together. Administration may be

intravenously, intra-arterial, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally. For *in vitro* studies the agents may be added or dissolved in an appropriate biologically acceptable buffer and added to a cell or tissue.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present such as, for example, anti-microbials, anti-oxidants, chelating agents, growth factors and inert gases and the like.

The compounds of general formula (I) are antimicrobial agents which are active, in particular but not limited to, against *Mycobacterium* including *Mycobacterium tuberculosis*, *M. avium intracellulare*, *M. fortuitum*, *M. abscessus* and rapid growing atypical Mycobacterial strains, *Nocardia*, particularly *Nocardia asteroides* and *N. nova*, *Staphylococcus* including *Staphylococcus aureus* and *S. aureus* (Coagulas-negative), *Streptococcus* spp. and *Enterococci* species. The compounds of general formula (I) are particularly useful in treating infections involving these organisms.

Generally, the terms "treating", "treatment" and the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing infection,

and/or may be therapeutic in terms of a partial or complete cure of an infection. "Treating" as used herein covers any treatment of, or prevention of infection in a vertebrate, a mammal, particularly a human, and includes:
5 preventing the infection from occurring in a subject that may have been exposed to the infectious agent, but has not yet been diagnosed as affected; inhibiting the infection, ie., arresting its development; or relieving or ameliorating the effects of the infection, ie., cause
10 regression of the effects of the infection.

According to a fifth aspect of the present invention there is provided a pharmaceutical composition comprising a compound of general formula (I) and a pharmaceutically acceptable carrier.

15 The pharmaceutical compositions according to one embodiment of the invention are prepared by bringing a compound of general formula (I) into a form suitable for administration to a subject using carriers, excipients and additives or auxiliaries.

20 Frequently used carriers or auxiliaries include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as
25 sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous
30 solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co., 1405-1412,1461-1487 (1975) and The National Formulary XIV., 14th ed. Washington:
35 American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The pH and exact concentration of the various components of the

pharmaceutical composition are adjusted according to routine skills in the art. See Goodman and Gilman's *The Pharmacological Basis for Therapeutics* (7th ed.).

The pharmaceutical compositions are preferably prepared and administered in dosage units. Solid dosage units include tablets, capsules and suppositories. For treatment of a subject, depending on activity of the compound, manner of administration, nature and severity of the disorder, age and body weight of the subject, different daily doses can be used. Under certain circumstances, however, higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administration of subdivided doses at specific intervals.

The pharmaceutical compositions according to the invention may be administered locally or systemically in a therapeutically effective dose. Amounts effective for this use will, of course, depend on the severity of the microbial infection and the weight and general state of the subject. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in situ* administration of the pharmaceutical composition, and animal models may be used to determine effective dosages for treatment of the cytotoxic side effects. Various considerations are described, e.g., in Langer, *Science*, 249: 1527, (1990). Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the

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manufacture of aqueous suspension. Such excipients may be suspending agents such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, which may be (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example,

heptadecaethylenoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as those mentioned above. The sterile injectable preparation may also a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents which may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of general formula (I) may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar

vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. Compounds of general formula (I) may also be administered 5 in combination with cyclodextrins for enhanced aqueous solubility.

Dosage levels of the compound of general formula (I) of the present invention will usually be of the order of about 0.05mg to about 20mg per kilogram body weight, 10 with a preferred dosage range between about 0.05mg to about 10mg per kilogram body weight per day (from about 0.1g to about 3g per patient per day). The amount of active ingredient which may be combined with the carrier materials to produce a single dosage will vary, depending 15 upon the host to be treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain about 1mg to 1g of an active compound with an appropriate and convenient amount of carrier material, which may vary from about 5 to 20 95 percent of the total composition. Dosage unit forms will generally contain between from about 5mg to 500mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a 25 variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In addition, some of the compounds of the 30 invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The compounds of the invention may additionally 35 be combined with other compounds to provide an operative combination. It is intended to include any chemically compatible combination of pharmaceutically-active agents,

as long as the combination does not eliminate the activity of the compound of general formula (I) of this invention.

According to a sixth aspect of the present invention there is provided a method of killing a 5 microorganism, comprising exposing said microorganism to a compound of general formula (I) as defined above.

Advantageously, although not limited to, the microorganism is selected from the group consisting of *Mycobacterium* including *Mycobacterium tuberculosis*, *M. avium intracellulare*, *M. fortuitum*, *M. abscessus* and rapid growing atypical *Mycobacterial* strains, *Nocardia*, particularly *Nocardia asteroides* and *N. nova*, *Staphylococcus* including *Staphylococcus aureus*, *Streptococcus spp.* and *S. aureus* (Coagulas-negative) and 15 *Enterococci* species.

Throughout this specification and the claims, the words "comprise", "comprises" and "comprising" are used in a non-exclusive sense, except where the context requires otherwise.

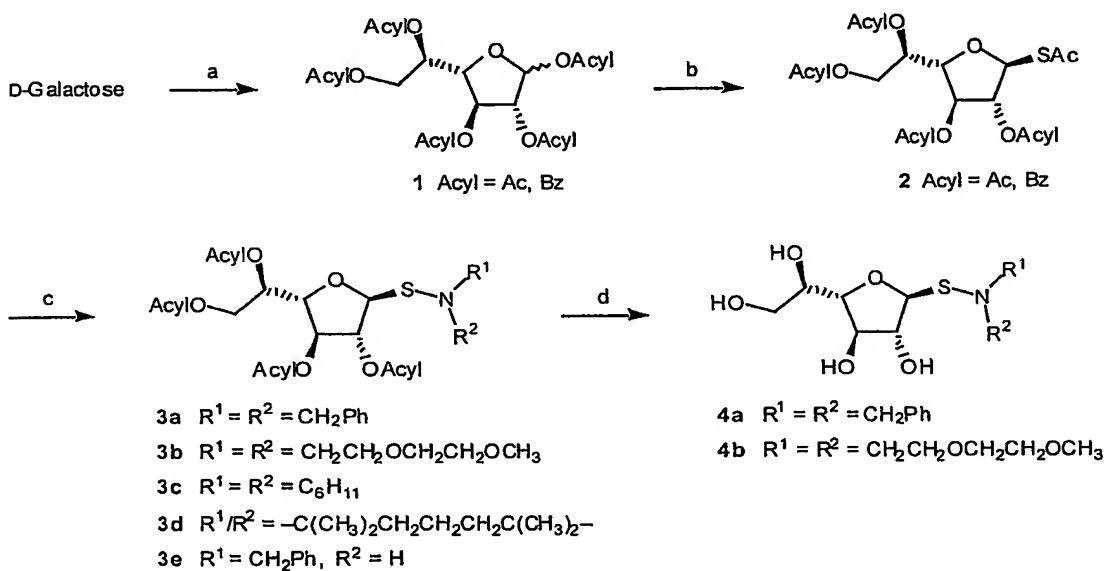
It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other 25 country.

Modes for Performing the Invention

The synthetic schemes employed to prepare compounds in accordance with preferred embodiments of the 30 invention are now described in more detail. The synthesis of protected (compounds 3a-f; Examples 1-5) and deprotected (compounds 4a,b; Examples 7&8) galactofuranosyl sulfenamides is shown in Scheme 1. For the preparation of these examples, 1,2,3,5,6-penta-O-35 acetyl-D-galactofuranose (compound 1, Acyl = acetyl; Bakinovskii et al., 1988) and 1-S-acetyl-2,3,5,6-tetra-O-benzoyl-1-thio- β -D-galactofuranose (compound 2, Acyl =

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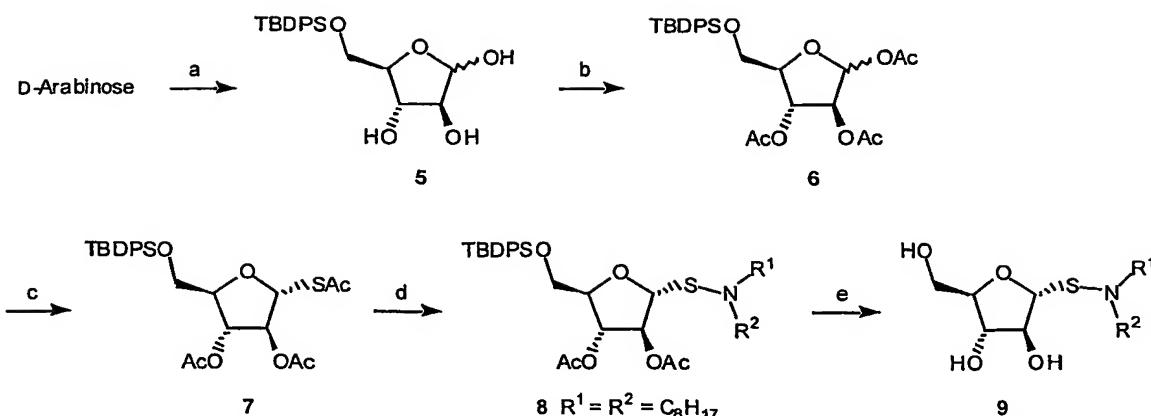
benzoyl; Owen and von Itzstein, 2000) were prepared according to known literature methods and are shown in Scheme 1 without modification. The synthesis of a protected (compound 8; Example 6) arabinofuranosyl sulfenamide is shown in Scheme 2. For the preparation of this example, 5-O-(*t*-butyldiphenylsilyl)-D-arabinofuranose (compound 5) was prepared according to known literature methods (Ikeda and Bando, 1995) and is shown in Scheme 2 without modification. All new compounds gave the expected spectroscopic data.



Scheme 1

15 Reagents and Conditions: a) Acyl = acetyl, according to Bakinovskii *et al.*, 1988; Acyl = benzoyl, according to D'Accorso *et al.*, 1983; b) SnCl₄ or BF₃.Et₂O, HSAc, CH₂Cl₂, 0 °C to rt, 1 to 6 h, N₂; c) BrCH(COOEt)₂, HNR¹R², DMF, THF, or MeOH, rt, 17 to 44 h; d) NaOMe, MeOH, rt, 2 h, N₂.

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Scheme 2

Reagents and Conditions: a) According to Ikeda and Bando, 1995;
 b) pyridine, Ac₂O, 0 °C, 1 h, N₂; c) BF₃.Et₂O, CH₂Cl₂, HSAC, rt,
 5 h, Ar; d) BrCH(COOEt)₂, HNR¹R², MeOH, rt, 3 h, Ar; e) i.
 TBAF, AcOH, THF, rt, 6 h, N₂; ii. NaOMe, MeOH, rt, 2 h, N₂.

1-S-Acetyl-2,3,5,6-tetra-O-acetyl-1-thio-β-D-
 galactofuranose (2, Acyl = acetyl):

1,2,3,5,6-Penta-O-acetyl-D-galactofuranose
 (1) (10.0 g, 25.6 mmol) was dissolved in anhydrous
 dichloromethane under N₂ and the solution cooled to 0 °C.
 Thioacetic acid (3.6 mL, 2 equivalents) and distilled
 borontrifluoride etherate (3.8 mL, 1.2 equivalents) were
 added dropwise and the reaction warmed to room
 temperature. After 6 hr the reaction was diluted with
 dichloromethane and quenched with saturated sodium
 bicarbonate. The organic phase was dried (Na₂SO₄),
 concentrated under reduced pressure, and the resulting
 yellow residue was chromatographed (3:2 hexanes/EtOAc) to
 give the product (2) (10.0g, 96%) as a yellow syrup. ¹H
 NMR (300 MHz, CDCl₃): δ 2.03, 2.04, 2.11, 2.12 (4 x 3H, 4 x
 s, 4 x OAc), 2.38 (3H, s, SAC), 4.07-4.23 (2H, m, H-4, H-
 6), 3.32 (1H, dd, J_{6',5} 4.2, J_{6',6} 12.0 Hz, H-6'), 5.07 (1H,
 m, H-2), 5.22 (1H, t, J_{2,1} ~ J_{2,3} 1.8 Hz, H-2), 5.37 (1H, m,
 H-5), 5.97 (1H, app. t, J_{1,2} 0.9 Hz, H-1).

Example 1

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N,N-Dibenzyl-S-(2,3,5,6-tetra-O-acetyl- β -D-galactofuranosyl)sulfenamide (3a) :

1-S-Acetyl-2,3,5,6-tetra-O-acetyl-1-thio- β -D-galactofuranose (2) (1.01 g, 2.50 mmol) was dissolved in methanol (75 mL). Diethylbromomalonate (630 μ L, 3.75 mmol) and dibenzylamine (1.20 mL, 6.3 mmol) were added and the reaction stirred at room temperature. After 44 h the solvent was removed and the residue purified by column chromatography on silica (1:1 EtOAc/hexanes) to yield the product (3a) (1.19 g, 86%) as a clear syrup. R_f 0.58 (1:2 EtOAc/hexanes). 1 H NMR (300 MHz, CDCl₃): δ 2.01, 2.05, 2.09, 2.15 (each 3H, s, OAc), 3.82 (4H, s, CH₂Ph), 4.17-4.40 (3H, m, H-4, H-6 and H-6'), 5.00-5.10 (2H, m, H-2 and H-3), 5.38 (1H, m, H-5), 5.48 (1H, d, $J_{1,2}$ = 3.0 Hz, H-1), 7.20-7.40 (10H, m, ArH); LRMS (ESI): *m/z* 559.9 [(M)⁺, 100%].

Example 2

N,N-Di(2-methoxyethoxyethyl)-S-(2,3,5,6-tetra-O-acetyl- β -D-galactofuranosyl)sulfenamide (3b) :

1-S-Acetyl-2,3,5,6-tetra-O-acetyl-1-thio- β -D-galactofuranose (2) (350 mg, 0.9 mmol) was dissolved in methanol (25 mL). Diethylbromomalonate (273 μ L, 1.7 mmol) and *N,N*-di(2-methoxyethoxyethyl)amine (479 mg, 2.4 mmol) were added and the reaction stirred at room temperature. After 19 h the solvent was removed under reduced pressure and the residue purified by column chromatography on silica (EtOAc) to yield the product (3b) (360 mg, 72 %) as a light golden oil. R_f 0.32 (EtOAc). 1 H NMR (300 MHz, CDCl₃): δ 1.91, 1.93, 1.96, 1.99 (4 x 3H, 4 x s, 4 x OAc), 3.08 (4H, t, J = 6 Hz, NCH₂CH₂), 3.23 (6H, s, OMe), 3.30-3.60 (12H, m, OCH₂), 4.00-4.25 (3H, m, H-5, H-6, H-6'), 4.92 (2H, m, H-2, H-3), 5.19 (1H, m, H-5), 5.29 (1H, d, $J_{1,2}$ 3.3 Hz, H-1).

35

Example 3

N,N-dicyclohexyl-S-(2,3,5,6-tetra-O-acetyl- β -D-

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galactofuranosyl)sulfenamide (3c) :

1-S-Acetyl-2,3,5,6-tetra-O-acetyl-1-thio- β -D-galactofuranose (2) (750 mg, 1.85 mmol) was dissolved in methanol (25 mL). Diethylbromomalonate (466 μ L, 2.78 mmol) and dicyclohexylamine (920 μ L, 4.63 mmol) were added and the reaction stirred at room temperature. After 90 min the solvent was removed and the residue purified by column chromatography on silica (1:2 EtOAc/hexanes) to yield the product (3c) (688 mg, 69%) as a clear syrup. R_f 0.68 (1:2 EtOAc/hexanes). 1 H NMR (300 MHz, CDCl₃) : δ 0.9-1.7 (20H, m, cyclohexyl), 1.95, 1.97, 2.01, 2.04 (each 3H, s, OAc), 2.62 (2H, m, cyclohexyl), 4.00-4.30 (3H, m, H-4, H-6 and H-6'), 4.94 (3H, m, H-1, H-2 and H-3), 5.28 (1H, m, H-5); LRMS (ESI) : *m/z* 565.8 [(M + Na)⁺, 100%].

15

Example 4

1-(2,2,6,6-Tetramethylpiperidine)-S-(2,3,5,6-tetra-O-acetyl- β -D-galactofuranosyl)sulfenamide (3d) :

1-S-Acetyl-2,3,5,6-tetra-O-acetyl-1-thio- β -D-galactofuranose (2) (472 mg, 1.12 mmol) was dissolved in methanol (15 mL) and tetrahydrofuran (15 mL). Diethylbromomalonate (293 μ L, 2.62 mmol) and 2,2,6,6-tetramethylpiperidine (782 μ L, 4.5 mmol) were added and the reaction stirred at room temperature. After 20 h the solvent was removed and the residue purified by column chromatography on silica (1:1 EtOAc/hexanes) to yield the product (3d) (356 mg, 61%) as a clear syrup. R_f 0.67 (1:1 EtOAc/hexanes). 1 H NMR (300 MHz, CDCl₃) : δ 1.10, 1.12, 1.21, 1.23 (each 3H, s, Me), 1.3-1.6 (6H, m, piperidine), 2.03, 2.04, 2.08, 2.12 (each 3H, s, OAc), 4.10-4.30 (3H, m, H-4, H-6 and H-6'), 5.01 (1H, dd, $J_{2,3}$ 6.3 Hz, $J_{3,4}$ 3.0 Hz, H-3), 5.13 (2H, m, H-1, H-2), 5.33 (1H, m, H-5); LRMS (ESI) : *m/z* 525.9 [(M + Na)⁺, 100%].

35

Example 5

N-Benzyl-S-(2,3,5,6-tetra-O-benzoyl- β -D-galactofuranosyl)sulfenamide (3e) :

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1-S-Acetyl-2,3,5,6-tetra-O-benzoyl-1-thio- β -D-galactofuranose (2) (330 mg, 0.50 mmol) was dissolved in methanol (15 mL). Diethylbromomalonate (256 μ L, 0.75 mmol) and benzylamine (218 μ L, 2.1 mmol) were added and the reaction stirred at room temperature. After 17 h the solvent was removed under reduced pressure and the residue purified by column chromatography on silica (1:1 EtOAc/hexanes) to yield the product (3e) (254 mg, 77 %) as a clear syrup. R_f 0.48 (1:1 EtOAc/hexanes). ^1H NMR (300 MHz, CDCl_3): δ 3.13 (1H, t, J 5.7 Hz, NH), 4.24 (2H, d, J 1.5 Hz, CH_2Ph), 4.85 (3H, m, H-6, H-6' and H-4), 5.71 (1H, d, $J_{1,2}$ 3.0 Hz, H-1), 5.74 (1H, app. t, $J_{1,2}$ 3.0, $J_{2,3}$ 2.1 Hz, H-2), 5.82 (1H, dd, $J_{2,3}$ 2.1, $J_{3,4}$ 4.8 Hz), 6.13 (1H, m, H-5), 7.2-7.7 (17H, m, *m,p*-ArH of benzoyl groups and ArH of Benzyl group), 7.9-8.2 (4 x 2H, 4x m, *o*-ArH of benzoyl groups).

Example 6

1,2,3-Tri-O-acetyl-5-O-(tert-butyldiphenylsilyl)- α/β -D-arabinofuranose (6):

5-O-(Tert-butyldiphenylsilyl)- α/β -D-arabinose (5) (2.10 g, 5.40 mmol) was dissolved in dry pyridine (20 mL) and stirred with acetic anhydride (20 mL, excess) at 0 °C for 1 h, and then at room temperature for 18 h under N_2 . After this time the solvent removed under reduced pressure and the residue was chromatographed on silica (4:1 hexanes/EtOAc) to furnish the product (6) (2.67 g, 96%) as a clear syrup. R_f 0.45 (4:1 hexanes/EtOAc). ^1H NMR (300 MHz, CDCl_3): δ 7.33-7.22 (m, 10 H, SiPh), 6.37 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1 β), 6.19 (bs, 1 H, H-1 α), 5.63 (dd, 1 H, $J_{3,4}$ 6.1, $J_{3,2}$ 7.2 Hz, H-3 β), 5.38 (m, 1 H, H-3 α), 5.33 (dd, 1 H, $J_{2,1}$ 4.8, $J_{2,3}$ 7.2 Hz, H-2 β), 5.21 (app d, 1 H, J 1.6 Hz, H-2 α), 4.24 (dd, 1 H, J 4.0, J 8.8 Hz, H-4 α), 4.12 (m, 1 H, H-4 β), 3.87 (m, 2 H, H-5 α and H-5' α), 3.81 (m, 2 H, H-5 β and H-5' β), 2.02-2.13 (6 x s, 18 H, 6 x OAc α and β), 1.07 (bs, 18 H, tert-butyl α and β).

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1-S-Acetyl-2,3-di-O-acetyl-5-O-(*tert*-butyldiphenylsilyl)-1-thio- α -D-arabinofuranose (7):

To a solution of 5-O-(*tert*-butyldiphenylsilyl)-1,2,3-tri-O-acetyl- α / β -D-arabinofuranose (6) (2.10 g, 4.08 mmol) in dry DCM (20 mL) at 0 °C, under Ar was added BF₃.OEt₂ (1.2 equivalents, 4.90 mmol). After 10 minutes thiolacetic acid (1.5 equivalents, 4.33 mL, 6.12 mmol) was added and the reaction was stirred for 5 h at room temperature under Ar. After this time the reaction was diluted with EtOAc (150 mL) and sat. aq. NaHCO₃ (150 mL). The organic layer was washed sat. aq. NaHCO₃ (150 mL) and aq. NaCl (150 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (3:1 hexanes/EtOAc) to furnish the product (7) (1.88 g, 87%) as a clear syrup. R_f 0.30 (4:1 hexanes/EtOAc). ¹H NMR (300 MHz, CDCl₃): δ 7.65-7.73 (m, 4 H, Si(Ph)₂), 7.34-7.46 (m, 6 H, Si(Ph)₂), 6.00 (bs, 1 H, H-1), 5.37 (m, 1 H, H-2), 5.25 (app t, 1 H, J 1.6 Hz, H-3), 4.14 (m, 1 H, H-4), 3.85 (m, 2 H, H-5 and H-5'), 2.39 (s, 3 H, SCOCH₃), 2.11 (s, 3 H, 1 x OCOCH₃), 2.02 (s, 3 H, 1 x OCOCH₃), 1.06 (s, 9 H, -C(CH₃)₃).

N,N-Dioctyl-S-(2,3-di-O-acetyl-5-O-[*tert*-butyldiphenylsilyl]-1-thio- α -D-arabinofuranosyl)sulfenamide (8, R¹ = R² = C₈H₁₇):

1-S-Acetyl-2,3-di-O-acetyl-5-O-(*tert*-butyldiphenylsilyl)-1-thio- α -D-arabinofuranose (7) (1.48 g, 2.79 mmol) was dissolved in dry methanol (20 ml). Diethylbromomalonate (938 μL, 5.58 mmol, 2 molar equiv.) was then added, and the mixture was stirred for 10 minutes at room temperature under Ar. Dioctylamine (3.36 mL, 11.15 mmol, 4 molar equiv.) was then added and the reaction stirred for 3 h at room temperature under Ar. The reaction was concentrated and the residue was taken up in EtOAc (100 ml), washed with sat. NaCl, dried (Na₂SO₄), filtered, and the solvent removed under reduced pressure. The residue was chromatographed on silica (6:1

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hexanes/EtOAc) to furnish the product (8) (1.30 g, 64%) as a pale yellow syrup. R_f 0.70 (4:1 hexanes/EtOAc). ^1H NMR (300 MHz, CDCl_3): δ 7.66-7.73 (m, 4 H, Si(Ph)₂), 7.33-7.47 (m, 6 H, Si(Ph)₂), 5.44 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1), 5.34 (dd, 1 H, $J_{3,4}$ 5.4, $J_{3,2}$ 3.2 Hz, H-3), 5.12 (dd, 1 H, $J_{2,3}$ 3.2, $J_{2,1}$ 4.0 Hz, H-2), 4.22 (m, 1 H, H-4), 3.85 (d, 2 H, J 3.9 Hz, H-5 and H-5'), 2.90 (m, 4 H, N(CH₂)₂), 2.05 (s, 6 H, 2 x OCOCH₃), 1.18-1.63 (m, 24 H, 12 x CH₂ dioctyl chain), 1.06 (s, 9 H, -C(CH₃)₃), 0.87 (m, 6 H, 2 x CH₃).

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General procedure for the deprotection of benzoate and acetate protecting groups:

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To a solution of the protected sulfenamide (0.5 mmol) in dry methanol (10 mL) under an atmosphere of N₂ is added one equivalent of sodium methoxide (1M solution in dry methanol). The reaction is left to stir at room temperature for 2 h. After this time the reaction is neutralized with Amberlite (H⁺) resin. The resin is removed by filtration, washed with methanol, and the solvent evaporated under reduced pressure. The residue is chromatographed on silica to yield the deprotected compound.

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General procedure for the deprotection of tert-butyldiphenylsilyl protecting groups:

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To a solution of the silyl protected sulfenamide (0.5 mmol) in dry THF (5 mL) at °C under an atmosphere of N₂ is added one and a half equivalents of tetrabutylammonium fluoride (1 M solution in THF) and acetic acid (0.1 mL). The reaction is left to stir at room temperature for 15 h, then additional acetic acid (0.5 mL) is added and the reaction is left to stir for a further 1 h. After this time the reaction mixture is evaporated under reduced pressure. The residue is chromatographed on silica to yield the desilylated compound.

Example 7

N,N-Dibenzyl-S-(β -D-galactofuranosyl)sulfenamide (4a) :

N,N-Dibenzyl-S-(2,3,5,6-tetra-O-acetyl- β -D-galactofuranosyl)sulfenamide (3a) (275 mg, 0.49 mmol) was de-O-acetylated to yield the product (4a) (47%) as a white solid. R_f 0.21 (8.5:1.5 EtOAc/methanol). 1H NMR (300 MHz, CD₃OD) : δ 3.60-3.80 (4H, m, H-2, H-5, H-6, H-6'), 3.90 (1H, dd, $J_{3,4}$ 7.8 Hz, $J_{3,4}$ 2.7 Hz, H-4), 4.07 (1H, m, H-3), 4.11 (4H, s, CH₂-Ph), 5.31 (1H, d, $J_{1,2}$ 5.1 Hz, H-1), 7.10-7.40 (10H, m, ArH); LRMS (ESI) : m/z 413.9 [(M + Na)⁺, 100%].

Example 8

N,N-Di(2-methoxyethoxyethyl)-S-(β -D-galactofuranosyl)sulfenamide (4b) :

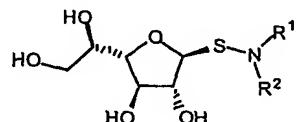
N,N-Di(2-methoxyethoxyethyl)-S-(2,3,5,6-tetra-O-acetyl- β -D-galactofuranosyl)sulfenamide (3b) was de-O-acetylated to give the product (4b) (55%) as a waxy solid. R_f 0.24 (14:5:1 EtOAc/methanol/H₂O). 1H NMR (300 MHz, D₂O) : δ 3.13 (4H, m, NCH₂CH₂), 3.38 (6H, s, OMe), 3.50-3.75 (15H, overlapping m, OCH₂, H-5, H-6 and H-6'), 3.79 (1H, t, $J_{3,4}$ 3 Hz, H-4), 3.92 (1H, dd, $J_{2,3}$ 7.5 Hz $J_{3,4}$ 3 Hz, H-3), 4.07 (1H, dd, $J_{1,2}$ 5.4 Hz $J_{2,3}$ 7.5 Hz, H-2), 5.20 (1H, d, $J_{1,2}$ 5.4 Hz, H-1); LRMS (ESI) : m/z 438.4 [(M + Na)⁺, 100%].

Biological DataExample 9

Inhibition of various bacteria by compound (4a) (R¹ = R² = CH₂Ph) is described in Table 1. Data for the previously reported compound N,N-dioctyl-S-(β-D-galactofuranosyl)sulfenamide (10) (R¹ = R² = C₈H₁₇; von Itzstein et al., 2003) is provided for comparison. The biological data were determined by a Zone Inhibition Assay method. Compounds were tested by spotting 100 µg of compound as a solution in methanol onto a sterile filter disc placed on a lawn of bacteria on the surface of an LB agar plate. After incubation at 37 °C for 72 h (M. smegmatis) or overnight (other species), the zone of inhibition was measured using an arbitrary scale: +++ = relatively large zone of inhibition, - = no zone of inhibition.

Table 1

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4a R¹ = R² = CH₂Ph10 R¹ = R² = C₈H₁₇

Organism tested	Compound	Zone of inhibition
<i>Mycobacterium smegmatis</i>	4a	++
	10	++
<i>Staphylococcus aureus</i>	4a	++
	10	++
<i>Streptococcus pyogenes</i>	4a	+
	10	++
<i>Bacillus subtilis</i>	4a	+
	10	+
<i>Enterococcus faecalis</i>	4a	+++
	10	++

Industrial Applicability

The compounds of general formula (I) are useful
5 as pharmaceuticals, particularly antimicrobial agents.

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